ARMY RESEARCH LABORATORY

Brain Structure-Function Couplings: Year 2 Accomplishments and Programmatic Plans

by J. M. Vettel, M. Vindiola, A. Dagro, P. J. McKee, R. H. Kraft, K. McDowell, and P. J. Franaszczuk

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Army Research Laboratory

Aberdeen Proving Ground, MD 21005

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J. M. Vettel, K. McDowell, and P. J. Franaszczuk
Human Research and Engineering Directorate, ARL

M. Vindiola
Dynamics Research Corporation
(Computing and Information Sciences Directorate, ARL)

A. Dagro
Weapons and Materials Research Directorate, ARL

P. J. McKee
Dynamic Science Incorporated
(Weapons and Materials Research Directorate, ARL)

R. H. Kraft
John Hopkins University Applied Physics Laboratory

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J. M. Vettel, M. Vindiola, A. Dagro, P. J. McKee, R. H. Kraft, K. McDowell, and P. J. Franaszczuk

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14. ABSTRACT
Research on brain structure-function couplings is a new topic area for the U.S. Army Research Laboratory (ARL), and the initial seed funding for the area was obtained in FY11 from ARL's Director's Strategic Initiative (DSI) program. This basic (6.1) neuroscience research effort aims to develop a multidisciplinary, multiscale understanding of the relationship between the brain's physical structure, its dynamic neurophysiological functioning, and human behavior. One of the broad, far-reaching science goals of this initiative is to understand the set of circumstances under which individual differences in brain structure can be leveraged to account for or predict variability in brain function or task performance at varying time scales. This required report summarizes Year 2 accomplishments and programmatic plans, and it was written for senior executives and managers to identify how this research area will transition from its third and final year of DSI funding to ARL core mission or customer funding.

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LAST UPDATED	1 May 2013	
INVESTIGATORS	**Name**	**Org/Div/Branch**
Principal Investigators	Jean Vettel, PhD Manuel Vindiola Amy Dagro P. Justin McKee Piotr Franaszczuk, PhD (Mentor)	HRED/SPD/TNB Dynamics Research Corp. (CISD) WMRD/PD/SPSB Dynamic Science Inc. (WMRD) HRED/Neuroscience ST
On-site Collaborators	Kaleb McDowell, PhD Alex Urban, PhD Stephen Gordon, PhD Antony Passaro, PhD Justin Kantner, PhD Joe McArdle, PhD Cameron Good, PhD Brian Henz, PhD Jason Sherwin, PhD Alex Herzog Sandhya Rawal Samantha Luo	HRED/SPD/TNB ORAU Postdoc DCS Corp DCS Corp Joint ORAU postdoc between ARL and Univ. of CA, Santa Barbara & Institute for Collaborative Biotechnologies ORAU Senior Researcher ORAU Senior Researcher CISD/CSD/SSB Joint ORAU postdoc between ARL and Columbia Univ ORISE Intern & Rensselaer Polytechnic Institute Graduate Student HRED/SPD/TNB ORISE Intern & Massachusetts Institute of Technology
Off-site Collaborators	Reuben Kraft, PhD Tim Verstynen, PhD Brian Kent Michael Miller, PhD Scott Grafton, MD Suvranu De, PhD Paul Sajda, PhD Troy Lau, PhD	John Hopkins Univ. Applied Physics Laboratory Carnegie Mellon Univ. Carnegie Mellon Univ. Graduate Student Univ. of CA, Santa Barbara & Institute for Collaborative Biotechnologies Univ. of CA, Santa Barbara & Institute for Collaborative Biotechnologies Rensselaer Polytechnic Institute Columbia University BAE Systems

DOCUMENT BACKGROUND

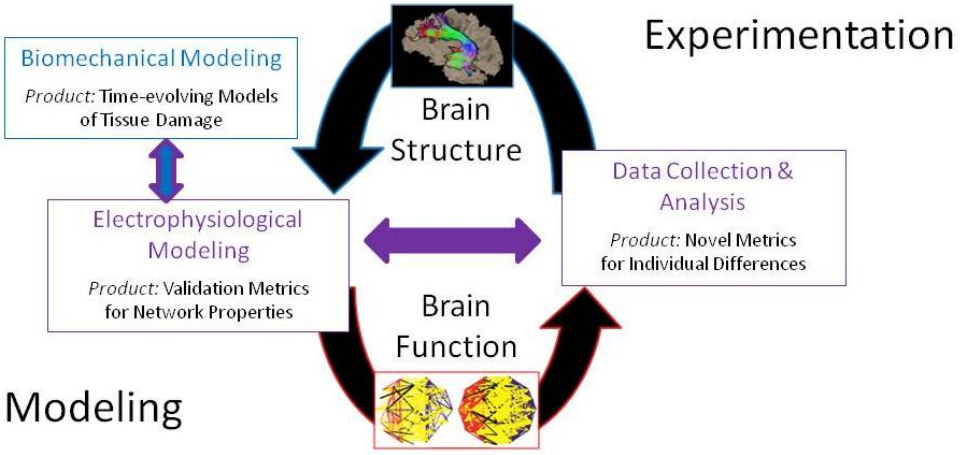
Research on brain structure-function couplings is a new topic area for the U.S. Army Research Laboratory (ARL), and the initial seed funding for the area was obtained in FY11 from ARL's Director's Strategic Initiative (DSI) program. The ARL Director issues an annual call for proposals, and ARL scientists and engineers submit proposals for a two to three year effort funded by the ARL Director's Office for newly emerging research areas. According to ARL guidance documents, successful DSI efforts will have the following characteristics: high-risk fundamental research that is collaborative across ARL and multidisciplinary in nature; strategic alignment with research areas identified by ARL leaders with high potential payoff to the Army mission by delivering unprecedented capabilities for the Soldier; and research topics that expand existing or establish new core competencies in support of ARL's major laboratory programs. Funded DSI proposals are intended to provide an opportunity to attract new researchers and allow for growth opportunities. If the DSI research is successful, it is then funded in follow-on years by an ARL core mission program or customer funding.

A formal "DSI Transition to Mission Plan" is required at the end of DSI Year 2 for senior executives and managers involved in funding and programmatic planning. It includes highlights of the scientific accomplishments as well as programmatic plans that detail how the DSI research will transition from its third and final year of DSI funding to ARL core mission or customer funding. This is a public release version of the transition to mission plan for a DSI effort to understand brain structure-function couplings.

DSI Overview

In FY11, a collaborative, cross-Directorate team of researchers began a new DSI to examine brain structure-function couplings. The effort aims to develop a multidisciplinary, multiscale understanding of the relationship between the brain's physical structure, its dynamic neurophysiological functioning, and human behavior. Here, brain structure refers to the architecture of the brain, namely, the grey matter regions in the brain and the white matter fiber tracts that connect them. Brain function indicates the neuron activity that enables communication between those regions. Combined, the individual variations in brain structure and function are thought to underlie individual differences in task performance and human behavior. One of the broad, far-reaching science goals of this initiative is to understand the set of circumstances under which individual differences in brain structure can be leveraged to account for or predict variability in brain function or task performance at varying time scales.

The cross-Directorate research program includes both modeling and experimentation efforts. The ongoing modeling efforts cover multiple spatial and temporal scales. In the Electrophysiological Modeling effort, we simulate functional oscillatory behavior for a brain region and examine how varying the structural connectivity between simulated brain regions changes the functional activity of the network. One project employs a neural mass model to simulate the oscillatory activity of a cortical column at each node, while another uses thousands of biophysical models of inhibitory and excitatory neurons connected into network to simulate the oscillatory activity at each node and interactions between nodes These two projects capture different spatial scales, but they both aim to uncover theoretical relationships between structural connectivity and the resulting functional connectivity. In addition, the models can be used to develop and test analysis methods since the underlying connectivity of the network is known. In the Biomechanical Modeling effort, we use finite element modeling and empirically derived formulas to relate how blast/blunt forces transfer to cellular death in neural tissue — ongoing efforts link cellular damage estimates with hypothesized changes to the structural connectivity between brain regions. These damaged structural networks can then be used as input for an electrophysiological model that simulates how the functional activity of the network changes based on the damaged structural connections.



The experimentation effort incorporates several neuroimaging methods to image structure (magnetization-prepared rapid gradient-echo [MPRAGE], diffusion imaging) and function (functional magnetic resonance imaging [fMRI], electroencephalography [EEG]) to derive structural and functional networks for an individual. The structural networks are based on white matter fiber tracts that connect brain regions, while the functional networks are derived from statistical dependencies of measured activity between regions. Ongoing research examines the sensitivity and reliability of reconstruction methods for deriving tractography as well as functional connectivity measures for deriving functional networks. This experimentation effort aims to develop metrics (e.g., network-level descriptions) that quantify differences among individuals in order to uncover empirical relationships between structure and function, and it then investigates when these metrics of individual differences can be used to predict variability in task performance.

Each of the three main research areas has been scoped to develop products to benefit ARL mission programs, as shown in blue and purple boxes in the figure above; however, the strength of this research program results from a focus on uncovering the fundamental relationships among brain structure, function, and behavior. In the long term, this foundational neuroscience knowledge can have broad-based applications to the Army, including improved strategies to assign a Military Occupational Specialty (MOS) to an enlisting Soldier, individual-specific training protocols to optimize skill acquisition, or analytic tools to triage, diagnose, and/or mitigate neural trauma. Our long-term emphasis targets understanding how fundamental brain structure-function-behavior relationships can improve Soldier performance through individual-specific neurotechnologies and enhance Soldier protection technologies to minimize neural injury.

The long-term vision of this research program is to develop time-evolving, predictive models of structure-function coupling that encompass how brain anatomy influences brain function and behavior (e.g., task performance). Overall, our research success will be measured by the accuracy and number of metrics for predicting Soldier function and/or performance as well as the resolution and accuracy of the biomechanical and electrophysiological models.

DSI Strategic Vision & Execution Strategy

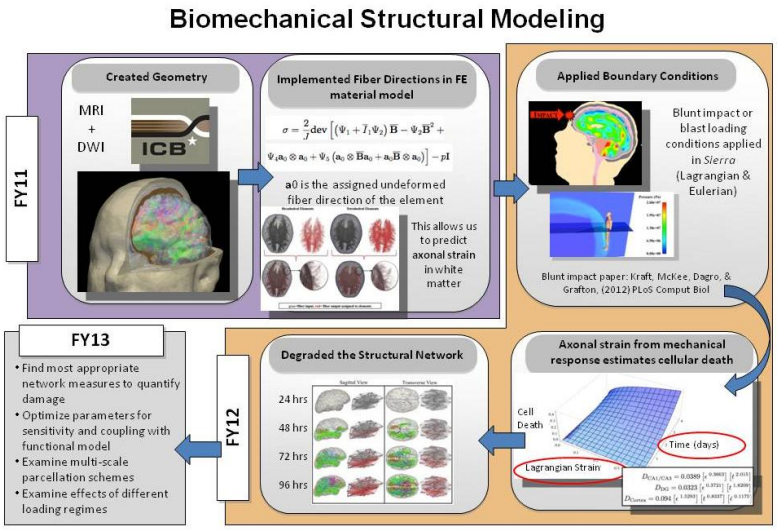
Over the past two decades, advancements in imaging technologies and computational analysis and modeling capabilities have provided new tools to study human activity across the fields of social, behavioral, and economic (SBE) sciences, including innovative approaches to unravel the basic principles of brain organization and function (e.g., Blue Brain Project, Allen Institute for Brain Science). In 2009, the White House published a report that outlines priority SBE research areas for Federal science agencies to maximize both scientific and policy gains from these recent advancements. This report outlined three foundational research themes, including one focused on the fundamental research to understand the structure and function of the brain. Similarly, our Army leadership has also prioritized research on the brain for strategic investment. In FY11, the annual Warfighter Outcome Analysis conducted by U.S. Army Training and Doctrine Command (TRADOC) identified neuroscience as a research area for targeted science and technology (S&T) investment to meet the Army's capability needs. More specifically, a top 12 Outcome listed a need to enhance Soldier performance by using network-level neuroscience approaches to improve performance in military environments, enhance cognitive fitness generally, and recover from combat stress or traumatic injury. In March 2011, the Assistant Secretary of Defense for Research and Engineering, Mr. Lemnios, included cognitive neuroscience as a top six disruptive basic research area in a brief to a House subcommittee on Emerging Threats and Capabilities.

In harmony with this guidance, we proposed a DSI in FY11 to build a multidisciplinary, basic (6.1) scientific program with interacting experimental and modeling research areas. Our program was designed to meet three primary considerations. First, the primary objective of the proposal was to articulate a basic science research niche for ARL that examines when individual differences in brain structure, function, and their couplings can explain or predict differences in Army-relevant task performance. Second, the research niche was scoped to ensure Army capability development. Specifically, we envision pathways that enable our basic science accomplishments to foster development of revolutionary Soldier neurotechnologies and Soldier protection. This ARL research niche aims to fulfill the Research Development and Engineering Command's (RDECOM) vision to know the state-of-the-art but envision and invest in developing the art of the possible. Finally, the third objective was a pragmatic goal to augment existing cross-Directorate ARL expertise and integrate the computational modeling expertise of the incoming Neuroscience ST. The proposal broadened and enhanced ARL's neuroscience capabilities by seeding efforts within HRED, WRMD, and CISD that could grow into viable mission-line or customer-funded efforts, including targeted involvement with the Army Research Office (ARO) and other Army partners.

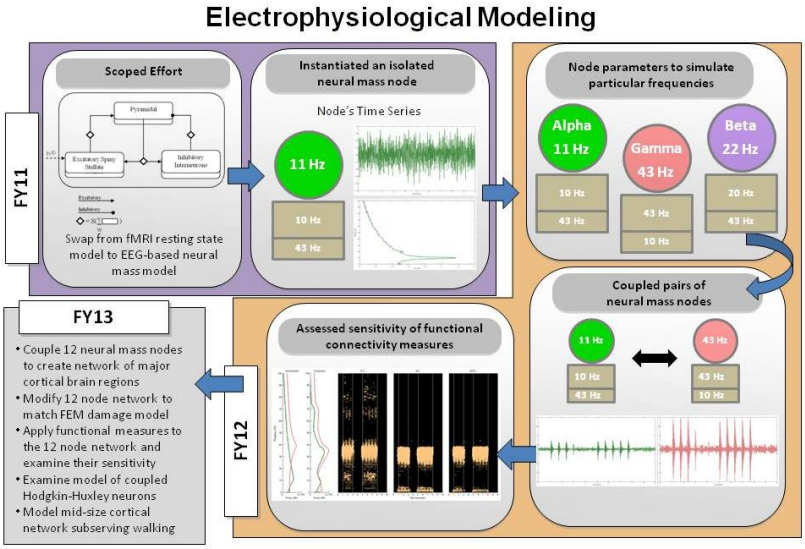
Consequently, our execution strategy in the first year emphasized the gradual allocation of mission funds to augment the DSI funding and begin to build research teams for our three main research areas (outlined above). Within WMRD, mission dollars were put on a 6.1 research line for blast and ballistic effects to the brain that paid for additional personnel to augment the DSI funds. Within HRED, the 6.1 line to understand the neural basis of neurocognitive performance was reframed to capture the strategic emphasis on brain structure-function couplings, and mission dollars were used to gradually augment the personnel working on this topic. Within CISD, a new postdoc with computational expertise was hired to extend their existing 6.1 line on time-evolving network systems to a novel domain, human brain networks. In addition to ARL mission funds, our group leveraged other Department of Defense (DOD) programs, including structural imaging research funded by the Defense Advanced Research Projects Agency (DARPA) and biomechanical modeling funded through an ARO Multidisciplinary University Research Initiative (MURI). We also wrote several proposals to secure competitive seedling funds under the Cognition and Neuroergonomics (CaN) Collaborative Technology Alliance (CTA) to foster new academic collaborations and obtain the critical structure-function-behavior datasets proposed as program deliverables in Year 3. The CaN CTA also has complementary research efforts that have contributed to our research success in the first two years. In short, we have steadily increased the amount of mission funding each year of the DSI to enable adequate resources to accomplish the ambitious aims from our proposal, and in FY12, both HRED and WMRD drafted a proposed budget to transition to full mission funding in FY14 at the conclusion of the DSI funding cycle. CISD will pursue customer funding to continue the research in subsequent years.

DSI SCIENTIFIC ACCOMPLISHMENTS

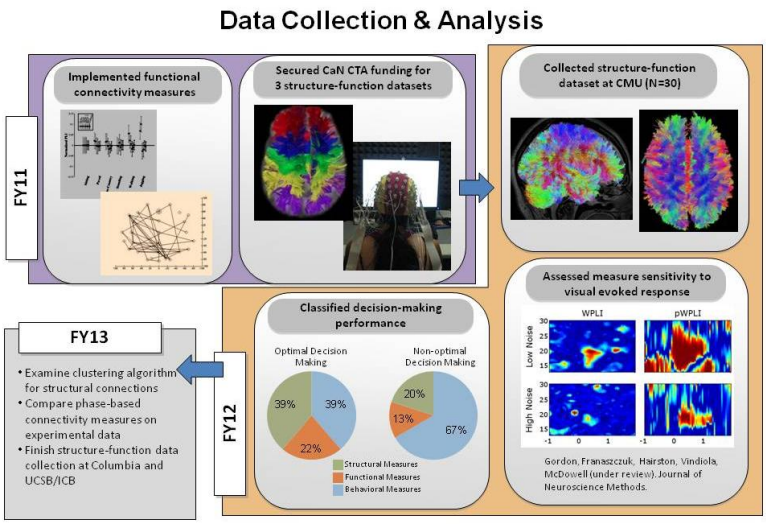
Biomechanical Structural Modeling: In FY11, the computational framework for a fiber-informed finite-element (FE) model was established for the implementation of the transverse isotropic material model representation of white matter tractography. By incorporating neuroimaging data from the Institute for Collaborative Biotechnologies (ICB), ARL created a three-dimensional (3-D) fiber-informed FE model of an individual. In the beginning of FY12, we published the mechanical response of the FE model compared to experimental data from the existing literature on blunt impact tests on cadavers. Subsequently, simulations were performed under blast-loading conditions using an export-controlled Department of Energy (DoE) FE code, Fortissimo, which makes use of two-way coupling of Lagrangian and Eulerian codes. Improvements to structural network modeling were made through the development of more robust software to couple physics-based simulation to a time-evolving structural network model. This model will continue to improve as injury thresholds from experimental data (ARO MURI research) advance our understanding of the relationship between mechanics and cellular injury mechanisms. Proof-of-concept edge degradation methods were developed to simulate loss of structural connection between regions of interest within the brain. This approach generates an injured network to capture the structural effect of loading to the head and brain, and it provides an estimate of location and scale of damage. Ongoing work will establish a link between a damaged structural network and the electrophysiological modeling effort to provide an approach to relate structural changes following simulated blast injury with electrophysiological changes, with a long-term goal of linking these changes to behavior.



Electrophysiological Modeling: In FY11, we reviewed the modeling literature and adopted a modeling framework that simulates dynamic oscillatory brain signals to ensure a tight link between the modeling and experimentation efforts. We instantiated and parameterized an isolated neural mass node to oscillate in the well-studied alpha frequency band. In early FY12, neural mass node parameters were determined to simulate dynamics similar to brain signals at additional, experimentally relevant frequencies (e.g., beta, gamma). Nodes were coupled together to create small-scale models of structural networks. We then created several sets of node pairs, and they were parameterized with time-evolving connectivity weights in order to examine the performance of functional connectivity measures. Three phase-based connectivity measures were examined, and overall, each measure was able to recover the temporal onset and offset of the synchronized communication, but they varied in their ability to recover the particular frequencies of the synchronization. Thus, we posit that the dynamics generated by coupled neural mass nodes are suitable for use with the functional connectivity measures identified in the experimentation effort.



Data Collection and Analysis: In FY11, efforts focused on implementing functional connectivity measures to compute time-evolving functional metrics and securing funds to collect the critical structure-function-behavior datasets. The FY11 annual report highlights two complementary results where the tested connectivity measures successfully captured task-relevant, brain network dynamics. We also secured competitive funding for three academic partners to co-design and collect structure-function-behavior datasets where participants perform Army-relevant tasks (e.g., target detection, decision making, multisensory integration). Success in FY12 built upon these first-year DSI efforts. A more extensive comparison of the performance of connectivity measures was published in FY12 that identified the resilence of the measures to parametrically-varied noise artifacts on both simulated data and well-studied visual evoked response in experimental data. These results indicate that time-evolving measures hold promise for understanding brain function in Army-relevant environments. The first of the three datasets funded in FY11 was collected, including an innovative diffusion-weighted imaging sequence that improved tractography reconstruction in areas of crossing fibers. The dataset also included several functional tasks (fMRI), and ongoing analyses examine how structure can be used to understand functional activation patterns. A third highlight from FY12 efforts was an analytic approach using machine learning methods (support vector machine [SVM]) to examine predictive relationships among a preliminary set of structural, functional, and behavioral metrics. This approach provides a method to examine predictive relationships of existing and novel individual difference measures and task performance.



RESEARCH SUMMARY

RESEARCH GOAL What is the science that we want to do?	**ARMY IMPACT** Why do we want to do this/what is the potential pay-off?
The overall vision of our research program is to develop time-evolving, predictive models of structure-function coupling that encompasses how brain anatomy influences brain function and behavior (e.g., task performance). The **biomechanical modeling effort** develops a model of structural changes at the level of brain tissue response to enhance Soldier protection technologies. We aim to link simulated damage at the tissue level with changes to the structural connectivity in the brain, and then use this damaged structural network as input to the electrophysiological model to examine how the structural damage modulates the simulated electrophysiological activity. Our five-year goal is to refine a proof-of-concept model of estimated structural damage and develop metrics to quantify this damage on a global scale that is sensitive to blast characterisitics. Our long-term goal is to develop predictive models of the time-evolving changes in brain structure, focusing on high-rate events such as blunt impact or blast trauma. Overall, our research success will be measured by the ability to produce predictive models of structural damage validated through experimental data and time-evolving models of injury and rehabilitation. The **electrophysiological modeling effort** develops dynamic models of interacting functional brain nodes configured based on a structurally defined network topology to uncover theoretical relationships between structure and function. We aim to understand dependencies between structural topology and functional oscillations in networks of simulated nodes. Our five-year goal is to explore the influence of spatial scale on structure-function relationships and develop approaches to quantify these relations in small-scale networks. Our long-term goal is to develop time-evolving predictive models that capture the influences of structure on function. Overall, our research success will be measured by the ability to produce predictive models of electrophysiological functioning based on individual-specific structural networks. Finally, the **experimentation effort** develops large-scale structural and functional network metrics to quantify individual differences in healthy adults, and the research examines when these metrics can predict differences in task performance. This experimentation effort collects structural, functional, and behavioral measures from individuals performing Army-relevant tasks to uncover empirical relationships among the three measures. Our five-year goal is to leverage individual differences in structural connectivity to understand individual differences in time-evolving functional metrics tailored to Army-relevant tasks. Our long-term goal is to develop integrative, network-level approaches to understand structure-function relationships as well as their predictive relationships with behavior. Overall, our research success will be measured by the accuracy and number of metrics for predicting Soldier function and/or performance as well as the resolution and accuracy of the biomechanical and electrophysiological models.	The criticality of this research is underscored by (1) a 2009 report from the White House that lists understanding brain structure function relationships as one of three foundational basic research themes, (2) a brief by Mr. Lemnios that lists cognitive neuroscience in the top six disruptive basic research areas, and (3) one of TRADOC's top 12 Warfighter Outcomes for FY11 that lists enhancing Soldier performance by using network-level approaches as a priority. Furthermore, our research addresses at least 10 FY11 Warfighter Outcomes, a list published by TRADOC to prioritize research to benefit the Soldier. As mentioned, one of the top 12 Outcomes states the need to leverage science to enhance Soldier cognitive abilities in military-relevant situations and accelerate recovery from brain injury. By collecting structural-functional-behavioral datasets of Army-relevant tasks, we aim to improve Soldier performance by developing functional measures and coupling these with structural differences to enable system designs that are matched to Soldier's abilities. If we are able to validate models of injury physics, we may help model interventions that can help accelerate recovery time and rehabilitation from brain injury. Additional FY11 Warfighter Outcomes highlight the need for improved technologies for training and restoring performance. If we are able to develop analysis constructs to link structure and function, we build the capability to decrease the time needed to train with shorter, more effective training programs tailored to an individual Soldier. We will have the capability to improve the tasking of individual Soldiers for more effective operations. This is just a sampling of how success of this research initiative has broad impacts that meet many of the stated Warfighter needs published annually by TRADOC. The immediate impact of this initiative is an in-house capability in computational neuroscience and brain modeling that provides the ability to leverage the rapid advancements of neuroimaging from the international neuroscience community and adapt them to address current Army challenges. We expect near-term impact with improved brain connectivity metrics and algorithms that quantify individual differences and can be used to improve Soldier-system performance with Soldier-specific neurotechnologies. We expect mid-term impact with models linking structure and function that can predict Soldier neurocognitive performance for a set of Army-relevant tasks, with likely applications within both healthy and clinical populations. We expect a far-term impact of enhanced armor that could minimize brain injury and increase survivability.

CURRENT STATE OF THE ART What has already been done (specify whether work was done here or elsewhere)?	**CHALLENGES** What are the key risks and technical challenges still to be overcome?
Biomechanical Modeling There is currently a lack of understanding about the injury process associated with primary blast injuries to the brain. The primary question that needs to be answered is how macroscopic forces get translated to the multiscale damage that induces traumatic brain injury. While connectivity damage has been examined by deleting network nodes in an "ad hoc" manner, ARL is the first to use a physics-based FE approach to alter the structural network behavior. **Electrophysiological Modeling** Several large-scale, multi-million dollar initiatives leverage advancements in supercomputing technology to revolutionize the tools and methods available to model the brain. The Blue Brain Project model replicates the activity of a rat's cortical column with plans to extend up to the rat's whole brain, and eventually, the human brain. The Allen Institute for Brain Science processes 5.5 terabytes of data/day to automate and integrate large-scale experiments, modeling, and theory. The Human Brain Project exploits innovations across multiple disciplines to accelerate the pace of big data neuroscience research by developing six integrated platforms, including ones on Neuroinformatics, Brain Simulation, and Neuromorphic Computing. These initiatives will fundamentally change the way we understand and model the brain. We are leveraging ARL's supercomputing (DOD Supercomputing Resource Center [DSRC]) resources to implement multiscale modeling efforts and ensure in-house expertise to identify and leverage modeling innovations for Army problems. **Experimentation** In recent years, significant advancements in the acquisition sequence and reconstruction methodologies have improved structural imaging capabilities. Specifically, we are leveraging a novel algorithmic approach, based on quantitative anisotropy, developed through a DARPA-funded initiative three years ago that substantially improves fiber reconstruction, especially crossing fiber tracts. Concordantly, in the Fall of 2010, the National Institutes of Health (NIH) awarded $40 million under the NIH Human Connectome Project to two research consortia. Each group will map the human brain's connections in high resolution, examining structural, functional, behavioral, genetic, and environmental factors. Our research niche will leverage these advancements and approaches to examine structure, function, and Army-relevant task performance within individuals in complex environments.	Across our research areas, three significant risks to this research initiative remain. First, even with recent innovations, the existing brain imaging technologies may not provide the resolution needed to uncover the predictive relationships among structure, function, and behavior if they exist. Second, it is still unknown at what length scale (or spatial scale) the brain must be studied to capture these predictive relationships, especially given the complexity of brain function underlying realistic behavior. Third, there is no established procedure to validate traumatic insults on isolated cells or animal models and scale these results to human brains. In addition to these overall risks to the research, we highlight three technical challenges specific to each research area: **Biomechanical Modeling** A: Bridge macroscopic brain mechanical response with cellular-level mechanical response to loading. B: Develop modeling concepts that can link short-term, i.e., blast physics, and long-term, i.e., injury physics, structural effects. C: Develop valid evolution laws for nucleation and growth of diffuse cellular damage. **Electrophysiological Modeling** A: Develop a data source to enable model development and validation. B: Uncover an appropriate dynamic structure-function modeling concept that is sensitive to changes in both function and structure. C: Parameterize a model on sparse functional data to maximize the predictive power of the model. **Experimentation** A: Develop a data source that provides sufficient information on both structural and functional brain states to enable concept development and validation. B: Develop sensitive and robust metrics to characterize structural and functional variability. C: Uncover analytic approaches to link structure, function, and behavior at varying timescales.

RESEARCH STRATEGY What is our technical approach/methodology?	**LEVERAGES** External Partnerships/Etc.
We mitigate the three significant risks to this research initiative discussed above in several ways. First, we have established collaborations to develop and obtain the highest-quality brain-imaging methodologies. We have also implemented concurrent modeling approaches at different scales and in different species within a multiscale framework that can accommodate expansion to alternative length scales if dictated by neuroscience breakthroughs. We also work in conjunction with academic colleagues funded by an ARO MURI on blast thresholds for injury in several preparations. In addition, our approach addresses the specified technical challenges. **Biomechanical Modeling** A: Develop multiscale structural dynamic model based off of theory and data available in the literature. B: Link explicit dynamic numerical models that handle transient blast physics with implicit quasi-static numerics that have arbitrary time discretization to resolve timescales associated with injury cascades. C: Leverage data from the ARO MURI (Blast-Induced Thresholds for Neuronal Networks) and existing literature to understand thresholds of injury and propose mathematical models that describe damage evolution. **Electrophysiological Modeling** A: Develop neurophysiological models to capture network-level descriptions of connectivity between brain areas (e.g., neural mass model and network of biophysical models of neurons). B: Instantiate and validate a single simulated node and a small network of interconnected nodes. C: Use structural data to parameterize a network of interconnected simulated brain areas. **Experimentation** A: Leverage and/or enhance both structural and functional imaging measures and develop database of these measures from the same individuals performing Army-relevant tasks. B: Leverage state-of-the-art advancements to quantify individual differences. C: Examine individual differences to identify variant and invariant relationships among structure, function, and behavior.	*Topic:* Experimental Datasets (structure, function, and behavior) *Partners:* CaN CTA ICB Carnegie Mellon University Columbia University *Topic:* High Performance Computing *Partners:* ARL DSRC *Topic:* Reduced Order Modeling *Partners:* Rensselaer Polytechnic Institute (RPI) *Topic:* High Rate Tissue Properties *Partners:* Institute for Soldier Nanotechnologies (ISN) Purdue University University of Florida *Topic:* Brain Injury Threshold *Partners:* ARO MURI Columbia University University of Pennsylvania Duke University *Topic:* Brain Injury Modeling *Partners:* Institute for Soldier Nanotechnologies (ISN) Columbia University University of Pennsylvania

DOCUMENTATION FOR FY11 (OCT2010-SEPT2011) AND FY12 (OCT2011-SEPT2012)

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Government Reports (FY11 & FY12):

- Kraft, R.H. & Dagro, A.M. Design and Implementation of a Numerical Technique to Inform Anisotropic Hyperelastic Finite Element Models using Diffusion Weighted Imaging. ARL-TR-5796. October 2011.
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Invited Cross-Service Briefs (FY11 & FY12):

- McDowell, MRMC, February 2011: "ARL's Neuroscience Strategic Research Initiative: Non-Injury"
- Chung, White House, OSTP, March 2011: "Materials for Physical and Trauma Protection Deep Dive"
- Kraft, ARO MURI, July 2011: "Computational Brain Biomechanics and Connections with the Human Connectome"
- Vettel, AFRL Modeling Group, December 2011: "Brain Structure-Function Couplings"
- Vettel, French Delegation, October 2011: "Brain Structure-Function Couplings"
- Dagro, Univ. of Pennsylvania, June 2012: "Connectome Neurotrauma Mechanics"
- McDowell, Human Systems Integration Deep Dive, July 2012: "Translational Neuroscience"
- McDowell, HRED Stakeholder's meeting, August 2012: "Translational Neuroscience"
- McDowell, TPA meeting with MRMC (Col Castro), September 2012: "Translational Neuroscience"

Awards (FY11 & FY12):

- Rawal (Mentor: Vettel): 2nd place undergraduate at ARL Summer Internship Symposium 2011
- McDowell, ARL Award for Leadership, 2011
- Kraft, Presidential Early Career Award for Scientists and Engineers 2011
- Vettel, Mentorship Award (on-the-spot) 2011
- Eidsmore (Mentor: Dagro and McKee): 1st place undergraduate at ARL Summer Internship Symposium 2012

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